



NTP
National Toxicology Program

NTP Dioxin Toxic Equivalency Factor Evaluation

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NTP Board of Scientific Counselors
Technical Reports Review Subcommittee Meeting

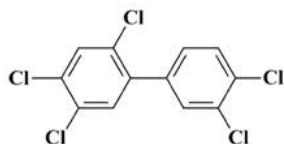
February 25, 2009



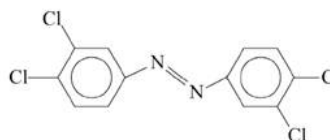


Introduction

- This meeting
 - 2,3',4,4',5-pentachlorobiohenyl (PCB118)-Technical Report 559
 - 3,3',4,4'-Tetrachloroazobenzene (TCAB) -Technical Report 558
- Part of ongoing program of work on dioxin-like compounds
 - Dioxin Toxic Equivalency Factor Evaluation
 - Summary of findings from the TEF Evaluation



PCB118



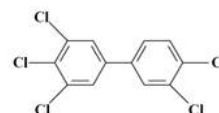
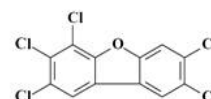
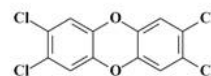
TCAB

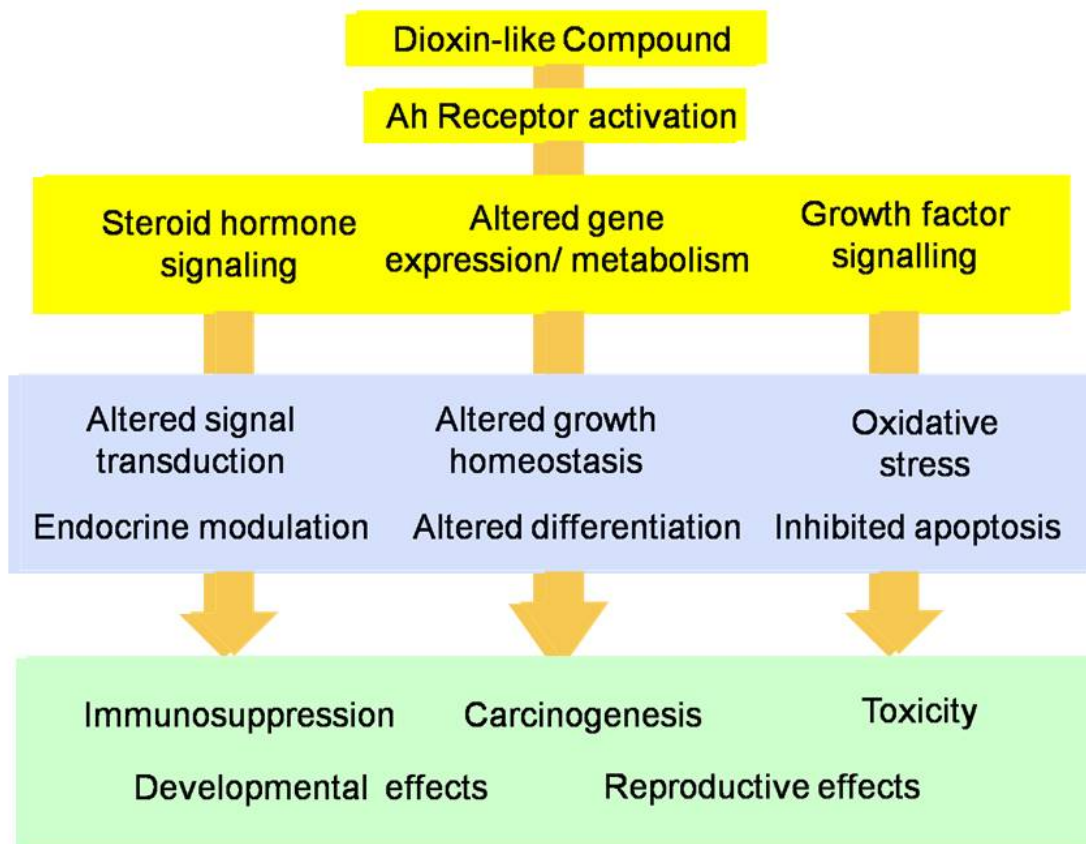


“Dioxin-like compounds”

- 2,3,7,8-tetrachlorodibenzo-p-dioxin
 - TCDD, “Dioxin”
- Polyhalogenated aromatic hydrocarbons
 - Structurally related class
- >90% human exposure is from food.
 - Long half-lives leads to persistent exposure
 - Episodic poisonings

2,3,7,8-tetrachlorodibenzo-p-dioxin







The NTP Dioxin TEF Evaluation

- Toxic equivalency factor (TEF) concept nominated for study
 - Humans constantly exposed to mixtures of DLCs
 - TEFs are assigned relative potency factors
 - TEFs used for cumulative risk assessment for exposure to mixtures of DLCs
 - TEF potency adjusted dose addition of all DLCs in the mixture
- Need to assess validity of concept of dose additivity using TEFs for health risk assessments for mixtures of DLCs
- NTP initiated a series of chronic carcinogenicity studies designed to evaluate interactions within mixtures of dioxin-like compounds.



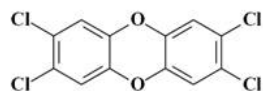
Goals of NTP Dioxin TEF Evaluation

- Relative potencies for cancer and non-cancer effects
- Interaction within a mixture of “dioxin-like” compounds
- Interaction of dioxin-like and non-dioxin-like polychlorinated biphenyls (PCBs)



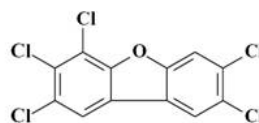
Test articles evaluated

2,3,7,8-tetrachlorodibenzo-p-dioxin



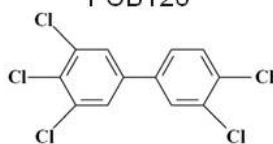
TEF=1.0

2,3,4,7,8-pentachlorodibenzofuran



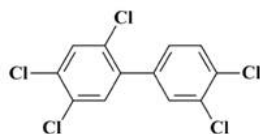
TEF=0.5

PCB126



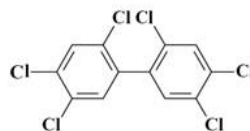
TEF=0.1

PCB118



TEF=0.0001

PCB153



No TEF



Study design

- Female Harlan Sprague-Dawley- 2 year studies
 - Interim evaluation at 14-, 31-, 53- weeks
 - Pathology, CYP450, thyroid hormones, tissue dosimetry
 - Special studies to provide samples for NIEHS grantees
- Phase I
 - TCDD, PeCDF, PCB126
 - Ternary mixture of these
- Phase II
 - PCB153
 - PCB126+ PCB153
 - PCB126+ PCB118
 - PCB118



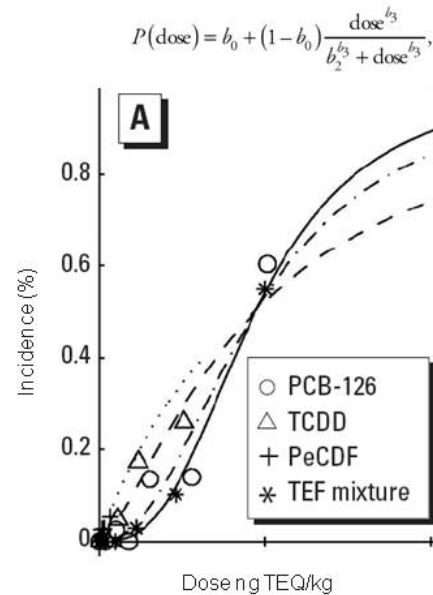
Phase I-summary results

- TCDD, PCB 126, PeCDF, and TEF mixture
- Expected increases in dioxin responses
 - Increases in CYP1 expression
 - Lower T4 and increased T3 for all studies
 - Increased TSH at early time points
- Hepatotoxicity
 - Increase in incidence and severity
- Non-neoplastic effects in multiple organs
- Increased incidence of neoplasms
 - Liver
 - Cholangiocarcinoma
 - Hepatocellular adenoma
 - Lung- cystic keratinizing epithelioma
 - Oral Mucosa- squamous cell carcinoma



Dose-additive carcinogenicity

- Dose response modeling of data from Phase I
 - Evaluation of slope and potency
 - Statistically based comparisons
- Dose additive combination of effects in the mixture
 - Cholangiocarcinoma
 - Hepatocellular adenoma
 - CKE
 - Gingival SCC
- Supports concept of using dose additivity for assessing cancer risk of dioxin mixtures

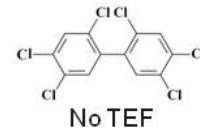




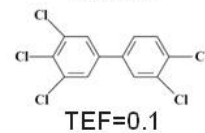
PCB studies

- PCB153
 - Equivocal evidence of carcinogenicity
 - rare cholangiomas
 - No increase in hepatocellular neoplasms
 - No increase in dioxin-like responses
- PCB 126 + PCB153 and PCB126 + PCB118
 - Same pattern of responses as PCB126 alone
 - Increased incidence of neoplasms in multiple organs
 - Liver, lung and oral cavity
 - Expected increases in dioxin-like responses
 - E.g. CYP1 expression
 - Increased incidence of non-neoplastic effects in multiple organs
 - lung, oral mucosa, pancreas, adrenal cortex, thyroid, thymus, kidney

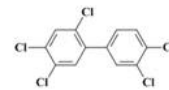
PCB153



PCB126



PCB118



Neoplasm	TCDD	PCB126	PeCDF	Mix	126/153	126/118	153
NTP Conclusion	Clear	Clear	Some	Clear	Clear	Clear	Equiv
Cholangiocarcinoma	++	++	+	++	++	++	+/-
Hepatocellular adenoma	++	+	+	++	++	++	
Hepatocellular carcinoma					++	++	
Cholangioma	+/-	+/-				+/-	
Hepatocholangioma	+/-	+			++	+/-	
Lung-Cystic keratinizing epithelioma	++	++	+/-	++	++	++	
Lung - Squamous cell carcinoma		+			++		
Gingival Squamous cell carcinoma	++	++	+		++	+	
Pancreas- acinus Adenoma/carcinoma	+/-		+	+/-	+		
Uterus - Squamous cell carcinoma	+				+/-		
Uterus-Carcinoma			+/-				
Adrenal Cortex -Adenoma /carcinoma		+/-					



Consistent effects across studies

- Consistent pattern of effects for the DLCs and mixtures
- Consistent effects
 - Cholangiocarcinoma and hepatocellular adenoma of the liver
 - Cystic keratinizing epithelioma of the lung
- Less consistency for other effects
 - Oral Mucosa
 - Pancreas
 - Uterus
- Pattern for DLCs clearly different from non-dioxin like PCB153



Not quite the end of the road

- This meeting
 - 2,3',4,4',5-pentachlorobiohenyl (PCB118)
 - 3,3',4,4'-Tetrachloroazobenzene (TCAB)
- Polychlorinated naphthalenes (66 and 67)
 - 90 days studies completed
- Hexachlorobenzene
 - 90 days studies completed
- Tg.AC Transgenics
 - Completed 26 week exposures in Tg.AC mouse model
 - Evaluation of PCB126, PeCDF and PCB126/PeCDF binary mixture
- Indole 3-carbinol
 - 2 year study ongoing

